ANDA 74-625

3 1 1996

Rosemont Pharmaceutical Corporation
Attention: Marcy Macdonald
301 S. Cherokee Street
Denver, CO 80223

Dear Madam:

This is in reference to your abbreviated new drug application dated February 16, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxybutynin Chloride Tablets USP, 5 mg.

Reference is also made to your amendments dated December 27, 1995 and March 15, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Oxybutynin Chloride Tablets 5 mg are bioequivalent, and therefore, therapeutically equivalent to those of the listed drug, Ditropan Tablets 5 mg of Hoechst Marion Roussel, Inc.. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-625
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-8/P.Savino
HFD-610/J.Phillips

Endorsement:

HFD-625/M.Shaikh/7-26-96
HFD-625/M.Smela/7-26-96
HFD-617/S.O'Keefe/CSO/R.West for/7-30-96
HFD-613/C.Holquist/7-30-96
HFD-613/A.Vezza/7-30-96
X:\new\firmsnz\rosemont\ltrs&rev\74625app.ltr
F/T by: bc/7-30-96

APPROVAL

NDC 0832-0038-10

Oxybutynin Chloride Tablets, USP

5 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

ROSEMONT

Manufactured by:
Rosemont Pharmaceutical Corporation
Denver, Colorado 80223
50-00038-10-00
Rev. 02-96

0832-0038-10

Each Tablet Contains:
Oxybutynin Chloride, USP 5 mg
Dosage: See package insert for full prescribing information.
Pharmacist: Dispense in tight, light-resistant container as defined in USP.
Keep this and all drugs out of the reach of children.
Store at controlled room temperature 15°-30°C (59°-86°F).

50000381000

Lot No.:
Exp.:

NDC 0832-0038-00

Oxybutynin Chloride Tablets, USP

5 mg

Caution: Federal law prohibits dispensing without prescription.

100 Tablets

ROSEMONT

Mfd. by: Rosemont Pharmaceutical Corp.
Denver, Colorado 80223
50-00038-00-00 Rev.02-96

0832-0038-00

Each Tablet Contains:
Oxybutynin Chloride, USP 5 mg
Dosage: See package insert for full prescribing information.
Pharmacist: Dispense in tight, light-resistant container as defined in USP.
Keep this and all drugs out of the reach of children.
Store at controlled room temperature 15°-30°C (59°-86°F).

50000380000

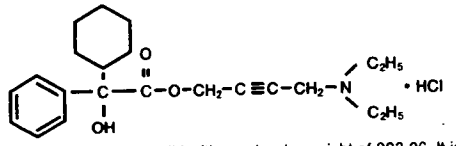
Lot No.:
Exp.:

APPROVED

15136-00

SEP 3 1996

DESCRIPTION
Chemically, oxybutynin chloride is the d,l (racemic) form of 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The molecular formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \cdot HCl$. The structural formula appears below:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.96. It is readily soluble in water and acids, but relatively insoluble in alkalis.

Each tablet, for oral administration, contains 5 mg of oxybutynin chloride. In addition, each tablet contains the following inactive ingredients: Calcium stearate, anhydrous lactose, and microcrystalline cellulose.

Therapeutic Category: Antispasmodic, anticholinergic.

CLINICAL PHARMACOLOGY
Oxybutynin chloride exerts direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin exhibits only one fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Oxybutynin chloride was well tolerated in patients administered the drug in controlled studies of 30 days duration and in uncontrolled studies in which some of the patients received the drug for two years. Pharmacokinetic information is not currently available.

INDICATIONS AND USAGE
Oxybutynin chloride tablets are indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria).

CONTRAINDICATIONS
Oxybutynin chloride is contraindicated in patients with untreated angle closure and in patients with untreated narrow anterior chamber angles since anticholinergic drugs may aggravate these conditions.

It is also contraindicated in partial or complete obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, megacolon, toxic megacolon complicating ulcerative colitis, severe colitis, and myasthenia gravis. It is contraindicated in patients with obstructive uropathy and in patients with unstable cardiovascular status in acute hemorrhage.

Oxybutynin is contraindicated in patients who have demonstrated hypersensitivity to the product.

WARNINGS
Oxybutynin chloride, when administered in the presence of high environmental temperature, can cause heat prostration (fever and heat stroke due to decreased sweating).

Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with oxybutynin chloride would be inappropriate and possibly harmful.

Oxybutynin chloride may produce drowsiness or blurred vision. The patient should be cautioned regarding activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug.

Alcohol or other sedative drugs may enhance the drowsiness caused by oxybutynin.

PRECAUTIONS
Oxybutynin chloride should be used with caution in the elderly and in all patients with autonomic neuropathy, hepatic or renal disease. Oxybutynin may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, and prostatic hypertrophy.

Administration of oxybutynin chloride to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at dosages up to approximately 400 times the recommended human dosage showed no evidence of carcinogenicity.

Oxybutynin showed no increase in mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae* and *Salmonella typhimurium* test systems. Reproduction studies in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility.

Pregnancy, *Teratogenic Effects*, Pregnancy Category B. Reproduction studies in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of oxybutynin chloride administered to women who are or who may become pregnant has not been established. Therefore, oxybutynin should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxybutynin chloride is administered to a nursing woman.

Pediatric Use. The safety and efficacy of oxybutynin chloride administration have been demonstrated for pediatric patients 5 years of age and older (see DOSAGE AND ADMINISTRATION). However, as there is insufficient clinical data for pediatric patients under age 5, oxybutynin is not recommended for this age group.

ADVERSE REACTIONS
Following administration of oxybutynin chloride, the symptoms that can be associated with the use of other anticholinergic drugs may occur:

Cardiovascular: Palpitations, tachycardia, vasodilatation.

Dermatologic: Decreased sweating, rash.

Gastrointestinal/Genitourinary: Constipation, decreased gastrointestinal motility, dry mouth, nausea, urinary hesitance and retention.

Nervous System: Asthenia, dizziness, drowsiness, hallucinations, insomnia, restlessness.

Ophthalmic: Amblyopia, cycloplegia, decreased lacrimation, mydriasis.

Other: Impotence, suppression of lactation.

OVERDOSAGE
The symptoms of overdosage with oxybutynin chloride may be any of those seen with other anticholinergic agents. Symptoms may include signs of central nervous system excitation (e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations), flushing, fever, nausea, vomiting, tachycardia,

heat prostration (fever and heat stroke due to decreased sweating).

Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with oxybutynin chloride would be inappropriate and possibly harmful.

Oxybutynin chloride may produce drowsiness or blurred vision. The patient should be cautioned regarding activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug.

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Other: Impotence, suppression of lactation.

OVERDOSAGE

The symptoms of overdosage with oxybutynin chloride may be any of those seen with other anticholinergic agents. Symptoms may include signs of central nervous system excitation (e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations), flushing, fever, nausea, vomiting, tachycardia, hypotension or hypertension, respiratory failure, paralysis, and coma.

In the event of an overdose or exaggerated response, treatment should be symptomatic and supportive. Maintain respiration and induce emesis or perform gastric lavage (emesis is contraindicated in precomatose, convulsive, or psychotic state). Activated charcoal may be administered as well as a cathartic. Physostigmine may be considered to reverse symptoms of anticholinergic intoxication. Hyperpyrexia may be treated symptomatically with ice bags or other cold applications and alcohol sponges.

DOSAGE AND ADMINISTRATION

Adults: The usual dose is one 5-mg tablet two to three times a day. The maximum recommended dose is one 5-mg tablet four times a day.

Children over 5 years of age: The usual dose is one 5-mg tablet two times a day. The maximum recommended dose is one 5-mg tablet three times a day.

HOW SUPPLIED

Oxybutynin Chloride Tablets USP are supplied in the following form:
As 5 mg–round, white, 5/16" diameter, single-scored tablets, debossed 832 and 38.
Dispense in tight, light-resistant containers as defined in the USP.
Store at controlled room temperature 15°- 30°C (59°- 86°).
Caution: Federal law prohibits dispensing without prescription.
Rev. 02-96

15136-00

Manufactured by
Rosemont Pharmaceutical Corporation
Denver, Colorado 80223

D J

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: **74-625**

FIRM: Rosemont Pharmaceutical Corporation, Denver, CO

DOSAGE FORM: Tablets

STRENGTH: 5 mg

DRUG: Oxybutynin Chloride Tablets USP

CGMP STATEMENT/EIR UPDATED STATUS:
EER submitted on 6-16-95 by M. Shaikh/D. Konigstein for the following facilities is pending

1. Rosemont Pharmaceutical Corporation
   301 South Cherokee Street
   Denver, CO 80223
   [Manufacturer for finished dosage form]

Acceptable 3/14/96

BIO STUDY:
Satisfactory per Farahnaz Nouravarsani's bio review completed on 6-28-96. Enclosed in vol. 2.1

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
USP drug product. MV is not required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Container used in the stability studies are identical to those listed in the container section.

Expiration granted: 24 months based on the stability data.

LABELING:
FPL: Satisfactory per Carol Holquist's review dated 3-25-96.

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Exhibit/Bio/Stability batch (lot # PD-021) size:
Tablets)

NDS Source: Referenced is satisfactory per S. Brown's review dated 2-22-96.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Bio and stability is same. Lot # PD-021

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
Rosemont's product batch size post-approval of this ANDA is:
tablets.

Manufacturing process for intended production size batch is same as used for the exhibit/bio/stability.

cc: ANDA 74-625
Division File
Field Copy
Endorsements:
HFD-625/M.Shaikh/7-26-96
HFD-625/M.Smela/7-26-96
x:\new\firmsnz\rosemont\ltrs&rev\74625app.pak
F/T by: bc/7-30-96

V I V

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-625

3. NAME AND ADDRESS OF APPLICANT
Rosemont Pharmaceutical Corporation
301 South Cherokee Street
Denver, CO 80223

4. BASIS OF SUBMISSION
Acceptable per CR # 1 completed by this reviewer.

The listed drug product is Ditropan^{R} Tablets, 5 mg by Marion Merrell Dow.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Oxybutynin Chloride Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 2-16-95
NC: 4-19-95
Major Amendment: 8-28-95 (Response to NA letter dated 6-25-95.
NC: 10-2-95
NC: 10-17-95
NC (Bio): 12-27-95 (Response to bio letter of 10-31-95).
* Minor Amendment: 3-15-96

FDA:
NA letter: 6-25-95 (Chemistry + Labeling)
Bio deficiencies letter: 10-31-95
NA letter: 2-22-96

10. PHARMACOLOGICAL CATEGORY
Anticholinergic

11. Rx or OTC
Rx

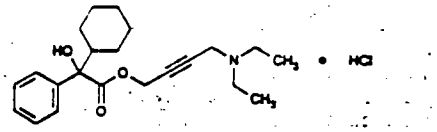
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCY
5 mg

15. CHEMICAL NAME AND STRUCTURE
Chemical Name: 4-(Diethylamino)2-butynyl(+/-)-a-phenylcyclohexaneglycolate hydrochloride

Structure:



16. RECORDS AND REPORTS
N/A

17. COMMENTS—
Rosemont has submitted adequate information with respect to chemistry and labeling. FPL - acceptable per review completed by C. Zimmermann on 3-25-96. Supporting DMF is adequate.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending satisfactory bio status and acceptable pre-approval EER.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
4-9-96

cc: ANDA 74-625
DUP File
Division File
Field Copy
Endorsements:
HFD-625/M.Shaikh/4-10-96
HFD-625/MSmela/4-10-96
x:\new\firmsnz\rosemont\ltrs&rev\74625rev.3
F/T by: bc/4-12-96

JUN 28 1996

Oxybutynin Chloride
5 mg, Tablets, USP
ANDA #74-625
Reviewer: F. Nouravarsani
74625SA.D95

Rosemont Pharmaceutical Corporation
Denver, CO
Submission Date:
December 27, 1995

REVIEW OF A BIOEQUIVALENCE STUDY AMENDMENT

INTRODUCTION:

Rosemont Pharmaceutical Corporation had submitted (February 16, 1995) a fasting, single dose bioequivalence study, and dissolution testing conducted on its test product, Oxybutynin Chloride Tablets, 5 mg and the listed reference product, Ditropan Tablets, 5 mg (N#17577-001) manufactured by Hoechst Marion RSSL (Marion Merrell Dow).

The study was found to be incomplet with 6 deficiencies. The deficiencies, the firm's responses, and the reviewer comments are as follows:

Deficiency #1:

There was discrepancy between the information submitted under Appendix IV, "Sample Handling Sheet", pages 140- 142, and "Copy of file:oxybut.dat". For example subjects #4, 5, 10, 11, 19, and 24 were not dosed at period I under "Sample Handling Sheet", but they were dosed at period I according to the "Copy of file:oxybut.dat". The firm should clarify, and submit a table summarizing the subjects in each period (1, 2, and 3) and each sequence.

Responce to Deficiency #1:

The firm has responded that the data under 'Sample Handling Sheets" are correct. The period assignment under the "file:oxybut.dat" was incorrect.

"The inappropriate assignment of period results in incorrect values for the statistical analysis of pharmacokinetic parameters. Therefore, the statistical analysis has been redone for both the analysis of the effect of group and the pooled groups for oxybutynin and desethyloxybutynin."

Reviewer Comment:

The response is acceptable.

Deficiency #2:

Subject #7, ., 0.0 hour (Set 7) showed a metabolite (page 320/1239). This sample was reassayed along with some other samples of this subject (set 35) due to failure of both low quality control samples. Although the reassayed value was bql, the firm should clarify, and check all the and data for any error.

Responce to Deficiency #2:

The firm responded that all for set 7, and from the other sets were reviewed and no errors were observed. However, it was unknown why there is a for metabolit at 0.0 hour. However, the repeated sample was BQL.

Reviewer Comment:

The firm's response is acceptable.

Deficiency #3:

Under Attachment D, "Freeze/Thaw Aliquoting Procedure" (page 1414/2339) was stated that study samples and quality control samples were placed "in a pan of shallow, warm water for approximately one hour prior to aliquoting". The firm should clarify whether the above procedure would have any effect on the stability of the oxybutynin or desoxybutynin.

Responce to Deficiency #3:

The firm responded that during thawing of the study samples, quality control (QC) samples were also included. There were no problem with the QC samples.

Reviewer Comment:

The response is acceptable.

Deficiency #4:

Under Method Validation (page 6/925) was stated that "signal to noise ratios of approximately 2:1 and 12:1 were measured at the limit of quantitation for oxybutynin and desethyloxybutynin, respectively". The firm should clarify how these ratios were set.

Responce to Deficiency #4:

The signal to noise was determined by deviding each component by the noise. The of desethyloxybutinin (36.5 mm) was divided by the of noise (3 mm).

Therefor signal to noise was 36.5/3 = 12:1. The of oxybutinin (5.5 mm) was divided by the of noise (3 mm). Therefor signal to noise was 5.5/3 = 2:1

Reviewer Comment:

The firm should be informed for future studies to increase the ratio of the signal to noise.

Deficiency #5:

Under Attachment F (Page 1427/2352) was stated that appropriate volumes of stock standard solution were used to prepare quality control samples. The firm was informed for the future studies that quality control samples should be prepared from different stock solution than the standard stock solution.

Responce to Deficiency #5:

The firm has responded that "two stock standard" were prepared. One solution is used for calibration standards, and the other one is used for preparation of quality control samples.

Reviewer Comment:

The response is acceptable.

Deficiency #6:

Under Analytical Notes (page 13/932) was stated that "Several sets demonstrated a "marked bend" to the desethyloxybutynin standard curve. As a results, values for the low quality control samples were elevated to unacceptable levels". The firm should identify the sets, and submit the unacceptable levels.

Responce to Deficiency #6:

The firm has responded that original value were not used because of unacceptability of the low quality controls. The following sets were 26, 27, 28, 36, and 37. The reassay sets were 40, 43, and 44.

Reviewer Comment:

The response is acceptable.

RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Rosemont Pharmaceutical Corporation on its Oxybutynin Chloride Tablets, 5 mg (lot #PD-021) comparing it to Ditropan Tablets, 5 mg (lot #K11372) has been found acceptable by the Division of

Bioequivalence.

2. The dissolution testing conducted by Rosemont Pharmaceutical Corporation on its Oxybutynin Chloride Tablets, 5 mg (lot #PD-021) is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE 6/26/96

Concur: _____ Date: 6/28/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/06-26-96/74625SA.D95

CC: ANDA #74-625 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Nouravarsani), Drug File, Division File.

OCT 18 1995

Oxybutynin Chloride
5 mg, Tablets, USP/N.F.
ANDA #74-625
Reviewer: F. Nouravarsani
74625SD.295

Rosemont Pharmaceutical Corporation
Denver, CO
Submission Date:
February 16, 1995

Review of Bioequivalence Study and Dissolution Testing

INTRODUCTION:

Rosemont Pharmaceutical Corporation submitted a fasting, single dose bioequivalence study, and dissolution testing conducted on its test product, Oxybutynin Chloride Tablets, 5 mg and the listed reference product, Ditropan Tablets, 5 mg (N#17577-001) manufactured by Marion Merrell Dow, Inc.

Oxybutynin Chloride is an antispasmodic and anticholinergic drug. It is indicated for the relief of symptoms of bladder instability associated with voiding. There are no Pharmacokinetic information available (PDR, 1995).

Oxybutynin Chloride is a synthetic tertiary amine with a pKa of 6.96. It is available commercially as a racemic mixture of 2 optical isomers (American Hospital Formulary Service, AHFS Drug Information, 1993).

The recommended dose for adult is one 5 mg tablet, 2 to 3 times a day. The maximum dose should not exceed 4 tablets (5 mg) per day. The children dose over 5 years of age is one 5 mg tablet, two times per day, and should not exceed three times per day (PDR, 1995).

OBJECTIVES:

1. Determine single dose bioequivalency of the test product, Oxybutynin Chloride Tablets, 5 mg, and the reference product, Ditropan Tablets, 5 mg under fasting conditions.

2. Compare dissolution testing conducted on the test and reference products.

BIOEQUIVALENCE STUDY:

Sponsor:
Manufacturer:
Clinical Facility:
, Principal Investigator:
Analytical Facility:
, Director:
Statistical Analysis:

Study Design:

A two-group, randomized, single dose, open-label, two-treatment, three-period crossover study was conducted in 38 subjects (Study Protocol No. 93032A/Study No. WARS-3184A). Thirty-eight (38) subjects were enrolled in order to obtain at least 36 evaluable subjects.

Protocol Exceptions:

The study design was deviated from the protocol for the following:

(a) thirty - eight subjects (36 plus 2 as potential alternate) were enrolled instead of 40 subjects (36 plus 4 as potential alternate).

(b) only 24 out of 38 enrolled subjects reported on the evening of the study date, October 08, 1993. The rest of the subjects started the study one week later, on October 16, 1993. It was stated that "due in large part to an unforeseen social activity on a local college campus, only 24 volunteers reported."

(c) subject #38 received 250 mL water at 1.33 hours (test, period II), because of dry mouth. Subjects were not allowed to drink water within 2 hours post-dose.

Treatments:

Treatment A (test Product): A single dose of Oxybutynin Chloride Tablets, 2X5 mg, lot #PD-021. Batch size tablets, manufacturing date: 3/93.

Treatment B (reference Product): A single dose of Ditropan Tablets, 2X5 mg, lot #K11372, expiration date: 5/96.

Subjects:

Thirty-eight (38) healthy, normal, non-smoking, male volunteers participated and completed the study in two Groups. The Group I, Twenty-four (24) subjects were dosed on October 9, 1993 (period I), and on October 16, 1993 (period II). The Group II, 14 subjects were dosed on October 16, 1993 (period II) and October 23, 1993 (period III).

The range of subject's age, weight, and height are summarized as follows:

Age: 18 - 35 years
Weight: 144 - 211 pounds
Height: 67 - 78 inches

Clinical Study Date:

Clinic Initiated: 10/09/93, 24 subjects, period I, group 1
10/16/93, 24 subjects, period II, group 1
10/16/93, 14 subjects, period I, group 2
10/23/93, 14 subjects, period II, group 2
Clinic Completed: 10/24/93
Washout period: 7 days

Housing, Fasting, Food and Fluid Intake:

All subjects were housed from the evening before the dose administration until after blood draw at 24 hour. They fasted overnight for 10 hours prior to the dosing and 4 hours after the dose. The dose was taken with 240 mL of water at room temperature. Standard meals and beverages were served at each period. Subjects were not allowed to drink water within 2 hours post-dose, then ad libitum to a maximum of about 2000 mL during the 24 hours.

Blood Samples:

A total of 19 blood samples (2x7 mL each) were collected for each subject at each period, at predose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hours postdose.

A total of 1,444 blood samples were collected for the study. The samples were shipped over the dry ice to the analytical laboratory by overnight express. The plasma samples were stored in a monitored freezer at (=)<-20° C until analysis.

Vital Signs:

Blood pressure and heart rate were determined at baseline, and at 2, and 4 hours following the administration of the dose. There were no clinically significant changes between the baseline and the measurements at 2 and 4 hours.

Analytical Procedures:

Statistical Analysis:

The data were analyzed using SAS - GLM procedure. The analysis of variance (ANOVA) was used to determine presence of Group effect and its interaction with the treatment. ANOVA was also conducted using all subjects as a single Group with 3 periods, and dropping the Group effect ($p>0.1$). The results of both models were reported.

The two one sided t-test procedure (90% confidence intervals) was used to compare the ln-transformed parameters of AUC(0-T), AUC(0-Inf), and C(Max) obtained from the test and reference products for both models.

RESULTS:

Oxybutynin:

The mean plasma oxybutynin concentrations are summarized in Table 1. There are no statistically significant differences between the concentrations at each sampling time ($p>0.05$) for the test and reference products except for the one at 10 hours ($p=0.0460$). Linear and semi-Ln Plots of the mean plasma concentrations of oxybutynin versus time for both test and reference products are shown in Figures I and II. The pharmacokinetic parameters are compared in Table 2.

The AUC(0-T) for the test product, 17.6 hr*ng/mL, is comparable with the AUC(0-T) of 18.8 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 19.0 hr*ng/mL, is comparable with the one obtained for the reference product, 20.4 hr*ng/mL.

The C(Max) for the test product, 10.4 ng/mL, is comparable with the C(Max) of 11.2 ng/mL for the reference product.

Mean test/reference ratios for AUC(0-T), AUC(0-Inf), and C(Max) were 102.1%, 101.4% and 115.9%, respectively Table 3.

The Group term and its interaction were not significant ($p>0.1$). Therefore, they were dropped, and analysis of variance was conducted using all subjects as a single Group with 3 periods. The results of the data analysis using ANOVA differed slightly in the presence or absence of the group effect, and the 90% CI were within the required range for both design.

There are no product or period effects for the parameters (Ln-transformed, $p=0.05$). There is sequence effect observed for the C(Max), Ln-transformed ($p=0.1$). The 90% confidence interval calculated for Ln-transformed AUC(0-T), AUC(0-Inf), and C(Max) are summarized in Table 2.

Desethyloxybutynin:

The mean plasma desethyloxybutynin concentrations are summarized in Table 4. There are no statistically significant differences between the concentrations at each sampling time ($p>0.05$) for the test and reference products.

Linear and semi-Ln Plots of the mean plasma concentrations of desethyloxybutynin versus time for both test and reference products are shown in Figures III and IV. The pharmacokinetic parameters are compared in Table 5.

The AUC(0-T) for the test product, 269.0 hr*ng/mL, is comparable with the AUC(0-T) of 278.6 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 277.5 hr*ng/mL, is comparable with the one obtained for the reference product, 286.7 hr*ng/mL.

The C(Max) for the test product, 96.7 ng/mL, is comparable with the C(Max) of 97.8 ng/mL for the reference product.

Mean test/reference ratios for AUC(0-T), AUC(0-Inf), and C(Max) were 100.2%, 100.3%, and 105.1%, respectively (Table 6).

The Group term and its interaction were not significant ($p>0.1$). Therefore, they were dropped, and analysis of variance was conducted using all subjects as a single Group with 3 periods. The results of the data analysis using ANOVA differed slightly in the presence or absence of the group effect, and the 90% CI were within the required range for both design.

There are no product, period ($p>0.05$), or sequence ($p>0.1$) effects observed for the above pharmacokinetic parameters (Ln-transformed). The 90% confidence intervals for Ln-transformed AUC(0-T), AUC(0-Inf), and C(Max) are summarized in Table 5.

Adverse Experiences:

The following table summarizes the possible drug related adverse

effects. The adverse experiences were transient, and were not unexpected.

Complaint	Subject #	Formulation
Dizzy	09	T
	29	R
Lightheaded	29	T
Cramp in lower right quadrant of abdomen	35	R
Bladder pressure	35	R
Cramping	35	R
Dry mouth	38	T

IN - VITRO STUDIES:

Dissolution Testing:

The dissolution testing was conducted on 12 units each of the test and reference products in 900 mL of water, apparatus 2 (paddle) with a rotation speed of 50 rpm. NLT of the labeled amount of oxybutynin chloride was dissolved in 30 minutes (Table 7). The conditions used by the firm is the same as those recommended in the USP 23, 1995.

Assay Potency:

The potency was 101.5% and 102.8% for the test and reference products, respectively.

Content Uniformity:

The content uniformity of the test product was 100.2% (CV=1.8%). The content uniformity of the reference product was 102.7% (CV=1.4%).

COMMENTS:

1. The 90% confidence intervals for the pharmacokinetic parameters (Ln-transformed) fall within the required range (80% - 125%) established by the Division of Bioequivalence.

2. Batch #PD-021 (test product) and #K11372 (reference product) were used for both, the bioequivalence study and the dissolution testing. The test product batch size was tablets.

3. No errors were found by spot checking of the calculations.

4. Thirty-eight (38) subjects completed the study in 2 Groups, which overlapped in time: Twenty-four (24) subjects in "Group I" were dosed on October 9 (period I) and October 16, 1993 (period II). Fourteen (14) subjects in "Group II" were dosed on October 16 (period II) and October 23, 1993 (period III). The Group term and its interaction with product was not significant ($p>0.1$). Therefore the data from all subjects were used as a single Group with 3 periods. The results of the data analysis using ANOVA differed slightly in the presence or absence of the group effect, and the 90% CI were within the required range for both designs.

5. Formulation of the test product, Oxybutynin Chloride Tablets, 5 mg is similar to formulation of the reference product, Ditropan Tablets, 5 mg (Table 8).

6. Rosemont had previously marketed a product of Oxybutynin Chloride Tablets, 5 mg (N70746-001, MAR 10, 1988). This product is listed under "Discontinued Drug Product List".

DEFICIENCIES:

1. There is discrepancy between the information submitted under Appendix IV, "Sample Handling Sheet", pages 140- 142, and "Copy of file:oxybut.dat". For example subjects #4, 5, 10, 11, 19, and 24 were not dosed at period I under "Sample Handling Sheet", but they were dosed at period I according to the "Copy of file:oxybut.dat". The firm should clarify, and submit a table summarizing the subjects in each period (1, 2, and 3) and each sequence.

2. Subject #7, [illegible] 2.0 hour (Set [illegible] shows a [illegible] or the metabolite (page 320/1239). This sample was reassayed along with some other samples of this subject (set 35) due to failure of both low quality control samples. Although the reassayed value was bql, the firm should clarify, and check all the [illegible] data for any error.

3. Under Attachment D, "Freeze/Thaw Aliquoting Procedure" (page 1414/2339) was stated that study samples and quality control samples were placed "in a pan of shallow, warm water for approximately one hour prior to aliquoting". The firm should clarify whether the above procedure would have any effect on the stability of the oxybutynin or desoxybutynin.

4. Under Method Validation (page 6/925) was stated that "signal to noise ratios of approximately 2:1 and 12:1 were measured at the limit of quantitation for oxybutynin and desethyloxybutynin, respectively". The firm should clarify how these ratios were set.

5. Under Attachment F (Page 1427/2352) was stated that appropriate volumes of stock standard solution were used to prepare quality

control samples. The firm should be informed for the future studies that quality control samples should be prepared from different stock solution than the standard stock solution.

6. Under Analytical Notes (page 13/932) was stated that "Several sets demonstrated a "marked bend" to the desethyloxybutynin standard curve. As a results, values for the low quality control samples were elevated to unacceptable levels". The firm should identify the sets, and submit the unacceptable levels.

RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Rosemont Pharmaceutical Corporation on its Oxybutynin Chloride Tablets, 5 mg (lot #PD-021) comparing it to Ditropan Tablets, 5 mg (lot #K11372) has been found incomplete by the Division of Bioequivalence.

2. The dissolution testing conducted by Rosemont Pharmaceutical Corporation on its Oxybutynin Chloride Tablets, 5 mg (lot #PD-021) is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the DEFICIENCIES 1-6.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE

Concur: _____ Date: _____
Keith Chan, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/08-25-95/74625SD.295

CC: ANDA #74-625 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Nouravarsani), Drug File, Division File

Table 1:

Mean (CV%) Plasma Concentrations (ng/mL) of Oxybutynin, N=38:

Time, hr	Test Product		Reference Product	
0.00	0.00	(---)	0.00	(---)
0.17	0.34	(171)	0.60	(197)
0.33	4.33	(103)	5.16	(128)
0.50	8.70	(60)	9.09	(90)
0.67	9.36	(50)	9.34	(63)
0.83	8.37	(46)	8.38	(53)
1.00	7.38	(44)	7.37	(50)
1.50	4.88	(42)	5.06	(51)
2.00	3.51	(40)	3.84	(47)
3.00	2.21	(41)	2.46	(78)
4.00	1.37	(45)	1.50	(80)
5.00	0.76	(46)	0.80	(82)
6.00	0.41	(79)	0.49	(89)
7.00	0.20	(147)	0.22	(139)
8.00	0.08	(238)	0.14	(180)
10.00	0.01	(616)	0.06	(266)
12.00	bql	(---)	0.01	(616)
16.00	bql	(---)	bql	(---)
24.00	bql	(---)	bql	(---)

Table 2:

Comparison of Mean (CV%) Oxybutynin Pharmacokinetic Parameters, and 90% CI Obtained for the Test and Reference Products, N=38:

Parameters	Test	Reference	90% CI Ln-trans.	%Ratio Mean
AUC(0-T) hr*ng/mL	17.6(41)	18.8(50)	86.3-107.4	96.3
AUC(0-Inf) hr*ng/mL	19.0(39)	20.4(48)	85.9-106.8	95.8
C(Max) ng/mL	10.4(50)	11.2(68)	83.9-118.0	99.5
T(Max) hr	0.65(26)	0.80(70)		
K(Elm) 1/hr	0.422(30)	0.426(37)		
T(1/2) hr	1.86(44)	2.18(103)		

Table 3: Ratio Analysis of the Parameters for Oxybutynin

	(Test/Reference) Percentage		
Subject	AUC(0-T)	AUC(0-Inf)	C(Max)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
Mean%	102.1	101.4	115.8
CV%	32.7	31.8	59.4
Range%			

Table 4:

Mean (CV%) Plasma Concentrations (ng/mL) of Desethyloxybutynin N=38:

Time, hr	Test Product		Reference Product	
0.00	00.00	(---)	00.00	(---)
0.17	00.61	(275)	00.94	(240)
0.33	22.17	(084)	23.09	(105)
0.50	64.09	(050)	65.27	(071)
0.67	84.73	(035)	83.71	(047)
0.83	89.63	(031)	85.13	(035)
1.00	84.78	(024)	81.49	(037)
1.50	66.01	(025)	65.60	(037)
2.00	54.26	(030)	56.20	(032)
3.00	40.57	(030)	42.37	(044)
4.00	28.04	(036)	29.68	(044)
5.00	19.63	(041)	22.02	(049)
6.00	13.51	(049)	14.77	(055)
7.00	09.00	(054)	09.58	(057)
8.00	06.03	(067)	06.85	(076)
10.00	02.33	(108)	02.68	(094)
12.00	01.01	(155)	01.03	(147)
16.00	bql	(---)	00.05	(616)
24.00	bql	(---)	bql	(---)

Table 5:

Comparison of Mean (CV%) Desethyloxybutynin Pharmacokinetic Parameters, and 90% CI Obtained for the Test and Reference Products, N=38:

Parameters	Test	Reference	90% CI Ln-trans.	%Ratio Mean
AUC(0-T) hr*ng/mL	269.0(31)	278.6(35)	91.5-104.7	97.9
AUC(0-Inf) hr*ng/mL	277.5(30)	286.7(35)	91.7-104.7	98.0
C(Max) ng/mL	96.68(26)	97.75(33)	91.8-109.7	100.4
T(Max) hr	0.82(27)	1.02(69)		
K(Elm) 1/hr	0.4017(18)	0.3978(17)		
T(1/2) hr	1.78(19)	1.79(18)		

Table 6: Ratio Analysis of the Parameters for Desethyloxybutynin

	(Test/Reference) Percentage		
Subject	AUC(0-T)	AUC(0-Inf)	C(Max)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
Mean%	100.2	100.3	105.1
CV%	21.7	21.4	32.2
Range%			

Table 7: In Vitro Dissolution Testing

Drug (Generic Name): Oxybutynin Chloride Tablets, USP
Dose Strength: 5.0 mg
ANDA: #74-625
Firm: Rosemont Pharmaceutical Corporation
Submission Date: February 16, 1995

I. Conditions for Dissolution Testing:

USP XXII Basket___ Paddle X RPM 50 No. Units Tested 12

Medium: water Volume: 900 mL

Reference Drug: Ditropan Tablets

Assay Methodology: Not stated

II. Results of In Vitro Dissolution Testing:

Sampling Times Lot minutes	Test Product: Oxybutynin Chloride # PD-021 Strength (mg) 5.0			Reference Product: Lot # K11372 Strength (mg) 5.0		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
05	50.5		(49.4)	36.8		(11.9)
10	87.9		(04.6)	84.5		(03.6)
15	94.0		(02.1)	90.0		(03.0)
20	95.0		(02.6)	91.4		(01.7)
30	95.8		(03.1)	94.5		(03.5)

Table 8: Formulation Comparison of 5 mg Tablets of Test (T) and Reference (R) products:

Ingredients	Test	Reference (b)
Oxybutynin Chloride	5.075(a)	5.00
Lactose		
Microcrystalline Cellulose		
Calcium Stearate		
FD&C Blue #1 Lake		

(a) 1.5% excess for moisture compensation
(b) From the Drug Product Reference (DPR) File

Figure I :

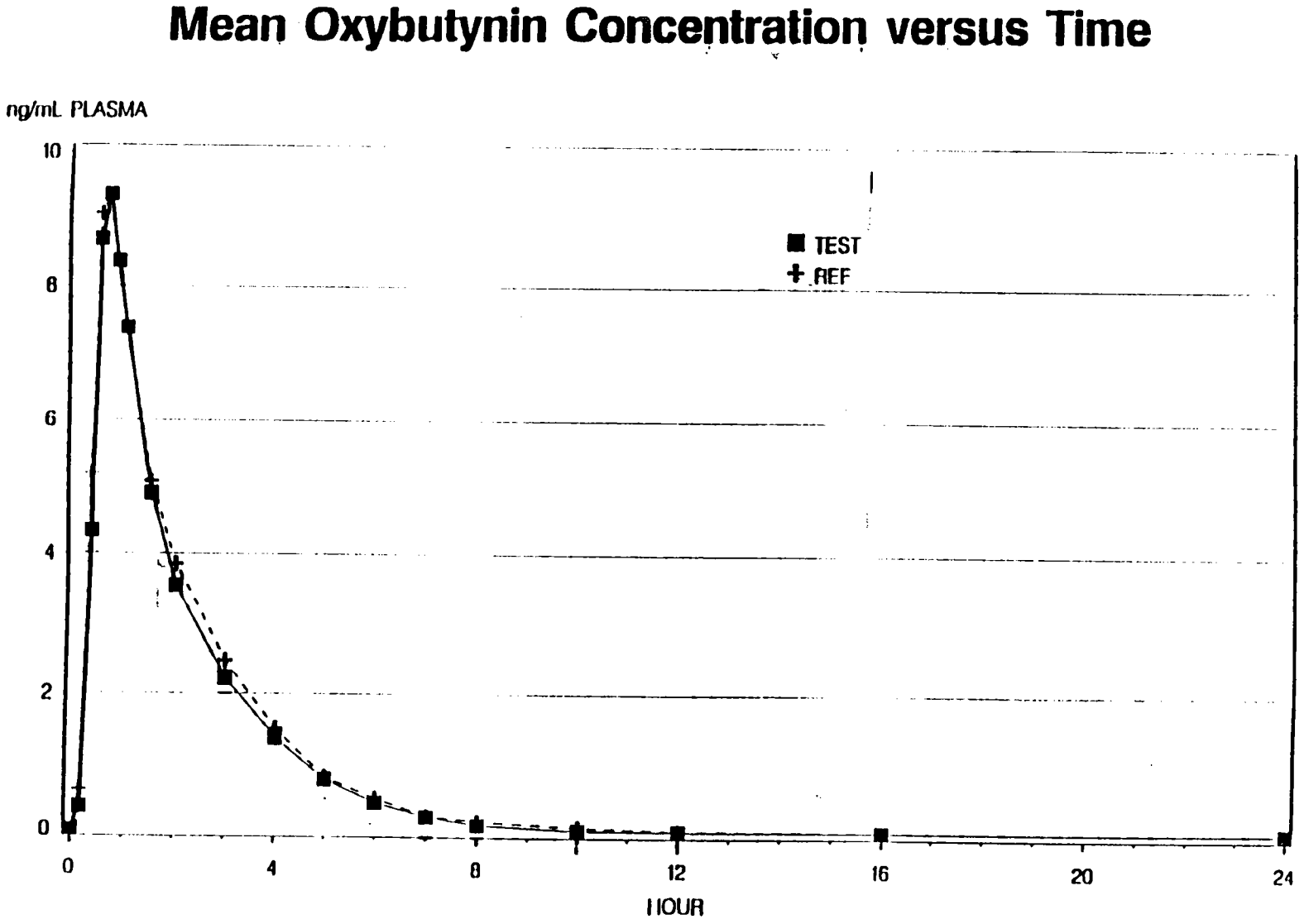

Mean Oxybutynin Concentration versus Time
ng/mL PLASMA
10
8
6
4
2
0
TEST
REF
0
4
8
12
16
20
24
HOUR

Figure II :

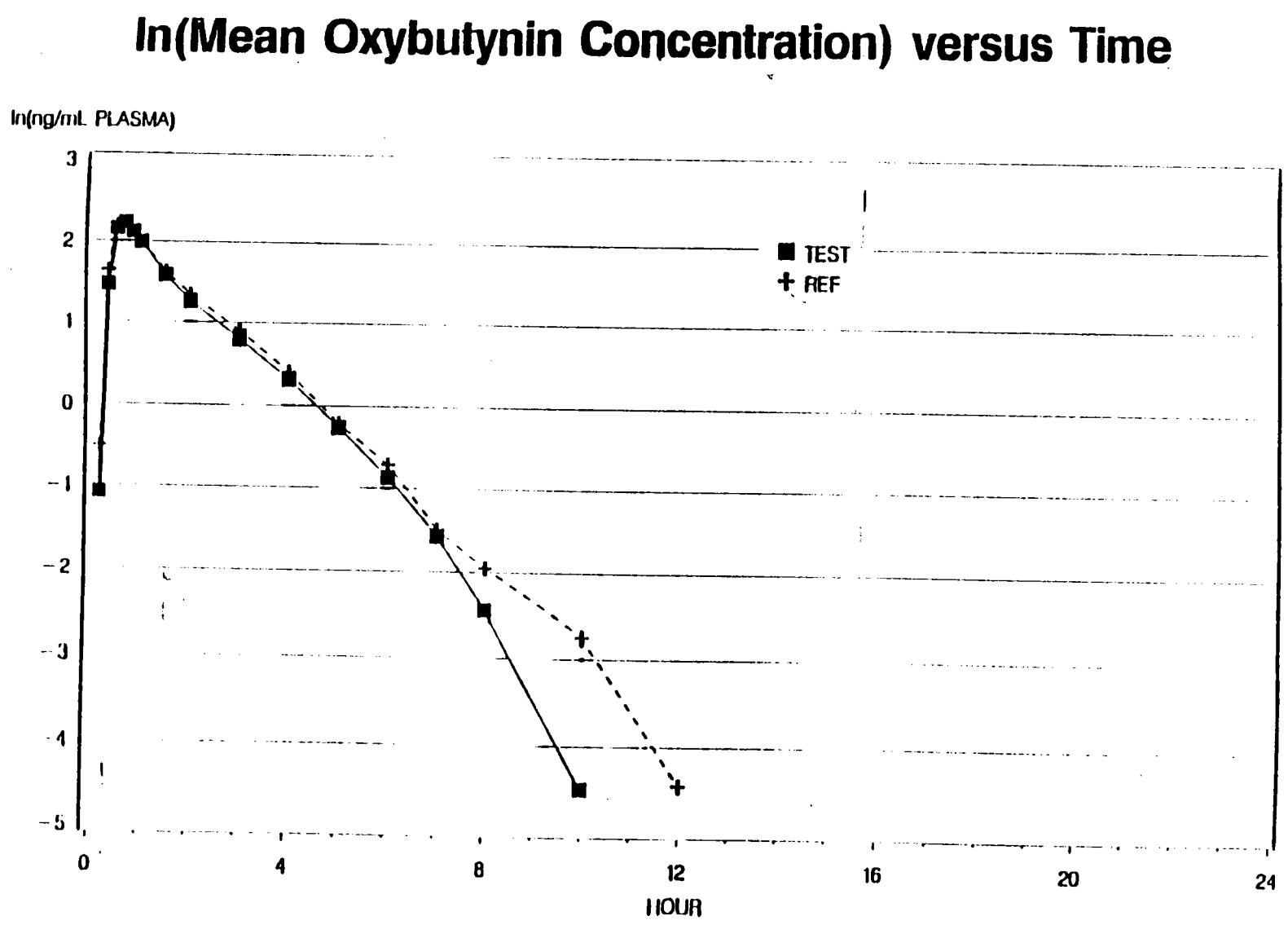

ln(Mean Oxybutynin Concentration) versus Time
ln(ng/mL PLASMA)
3
2
1
0
-1
-2
-3
-4
-5
TEST
REF
0
4
8
12
16
20
24
HOUR

Figure III :

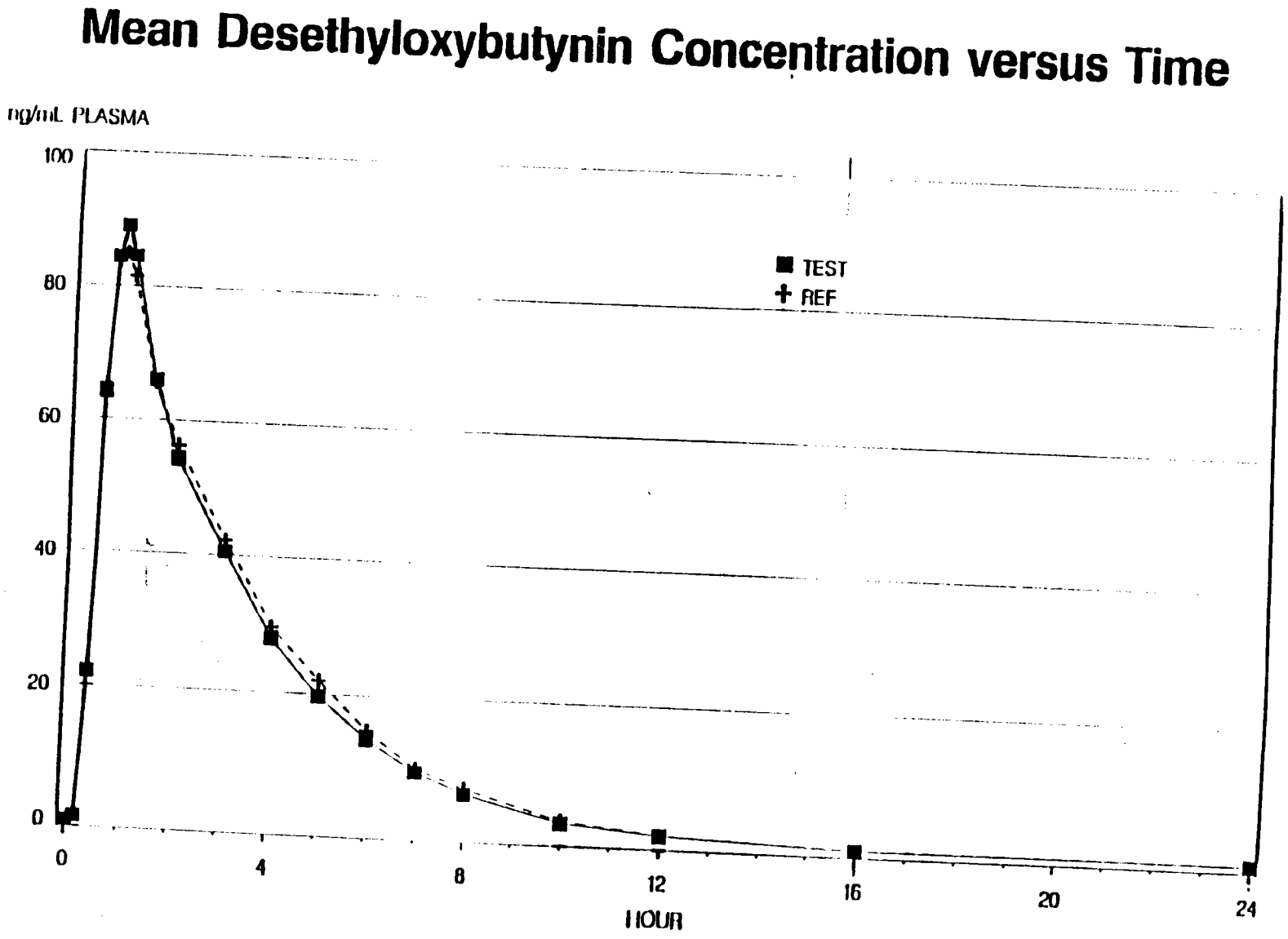

Mean Desethyloxybutynin Concentration versus Time
ng/mL PLASMA
100
80
60
40
20
0
TEST
REF
0
4
8
12
16
20
24
HOUR

Figure IV :

ln(Mean Desethyloxybutynin Concentration) versus Time